Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Subclinical hypothyroidism in the infertile female population: a guideline.

Bibliographic Source(s)

Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. Fertil Steril. 2015 Sep;104(3):545-53. [62 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the level of evidence (Level I-III) and the strength of the recommendation (Grade A-C) are given at the end of the "Major Recommendations" field.

Summary

- Subclinical hypothyroidism is defined as a thyroid-stimulating hormone (TSH) level greater than the upper limit of normal range (4.5–5.0 mIU/L) with normal free thyroxine (FT4) levels.
- The normal reference range for TSH changes in pregnancy. The upper limit of normal in most laboratories is 4 mIU/L for nonpregnant women and 2.5 mIU/L in the first trimester of pregnancy.
- This guideline was conducted because it is controversial whether or not to use first-trimester pregnancy thresholds for upper limit of TSH (i.e., >2.5 mIU/L) to diagnose and treat subclinical hypothyroidism (SCH) in women with infertility who are attempting pregnancy.
- There is insufficient evidence that SCH (defined as TSH >2.5 mIU/L with a normal FT4) is associated with infertility.
- There is fair evidence that SCH, defined as TSH levels >4 mIU/L, is associated with miscarriage, but insufficient evidence that TSH levels 2.5–4 mIU/L are associated with miscarriage.
- There is fair evidence that treatment of SCH when TSH levels are >4 mIU/L is associated with improved pregnancy rates and decreased miscarriage rates.
- There is fair evidence that SCH when TSH levels are >4 mIU/L during pregnancy is associated with adverse developmental outcomes; however, treatment did not improve developmental outcomes in the only randomized trial.
- There is fair evidence that thyroid autoimmunity is associated with miscarriage and fair evidence that it is associated with infertility.

Levothyroxine treatment may improve pregnancy outcomes in women with positive thyroid antibodies, especially if the TSH level is over 2.5 mIU/L.
- There is good evidence against recommending universal screening of thyroid function during pregnancy.

Recommendations

- Currently available data support that it is reasonable to test TSH in infertile women attempting pregnancy. If TSH concentrations are over the nonpregnant lab reference range (typically >4 mIU/L), patients should be treated with levothyroxine to maintain levels below 2.5 mIU/L. (Grade B)
- Given the limited data, if TSH levels prior to pregnancy are between 2.5 and 4 mIU/L, management options include either monitoring levels and treating when TSH >4 mIU/L, or treating with levothyroxine to maintain TSH <2.5 mIU/L. (Grade C)
- During the first trimester of pregnancy it is advisable to treat when the TSH is >2.5 mIU/L. (Grade B)
- While thyroid antibody testing is not routinely recommended, one might consider testing anti-thyroperoxidase (TPO) antibodies for repeated TSH values >2.5 mIU/L or when other risk factors for thyroid disease are present. (Grade C)
- If anti-TPO antibodies are detected, TSH levels should be checked and treatment should be considered if the TSH level is over 2.5 mIU/L. (Grade B)

Definitions

Level of Evidence

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Strength of Evidence

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Clinical Algorithm(s)

None available

Scope

Disease/Condition(s)

- Thyroid dysfunction (subclinical hypothyroidism)
- Infertility

Note: The classic definition of subclinical hypothyroidism is a thyrotropin (TSH) level greater than the upper limit of normal range (4.5-5.0 mIU/L) with normal free thyroxine (FT4) levels.

Guideline Category

Evaluation

Screening

Treatment

Clinical Specialty

Endocrinology

Internal Medicine

Obstetrics and Gynecology

Intended Users

Physician Assistants

Physicians

Guideline Objective(s)

To review the risks and benefits of treating subclinical hypothyroidism in female patients with a history of infertility and miscarriage, as well as obstetrical and neonatal outcomes in this population

Target Population

Female patients with a history of infertility and miscarriage

Interventions and Practices Considered

1. Testing thyroid-stimulating hormone (TSH) (monitoring and maintaining levels, typically between 2.5 and 4 mIU/L)
2. Levothyroxine
3. Testing anti-thyroperoxidase (TPO) antibodies for repeated TSH values

Major Outcomes Considered

- Pregnancy
- Implantation
- Live births
- Miscarriage
- Infertility
- Adverse pregnancy outcomes

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search

A systematic literature search was performed using a combination of the following keywords: subclinical hypothyroidism, diagnosis, level, criteria, pregnancy loss, abortion, miscarriage, infertility, pregnancy, baby, fetus, birth defect, delivery, antibody, elevated thyroid-stimulating hormone (TSH), live-birth rate, preeclampsia, pregnancy rate, complication, death, and demise.

The search was restricted to MEDLINE citations of human subject research published in the English language from 1966 to March 2014. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a procedure correlated with outcome measure (pregnancy, implantation, or live-birth rates), meta-analyses, and relevant articles from bibliographies of identified articles.

Inclusion/Exclusion Criteria

Include relevant articles with:

- Human subjects
- English language
- Level 2-3 evidence and above
- Systematic reviews
- Articles that define subclinical hypothyroidism as TSH <5 mIU/L

Exclude articles:

- Off topic
- Level 3 evidence (opinion, nonsystematic review, case report, very small case series)
- Non-English articles
- Without clearly defined subclinical hypothyroidism or a definition of >5 mIU/L

Database Searched - PubMed

Number of Source Documents

- Total selected from all three searches: 134+213+15+47=409
- Total raw from all three searches: 829+1340+47=2216

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The quality of the evidence was evaluated using the grading system found in the "Rating Scheme for the Strength of the Recommendations" field and is assigned for each reference in the bibliography (see the original guideline document).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The literature was reviewed to answer the following questions:

- How to diagnose subclinical hypothyroidism (SCH)?
- Does untreated SCH contribute to miscarriage rates?
- Does untreated SCH contribute to infertility?
- Does treatment of SCH improve miscarriage rates?
- Does treatment of SCH improve live birth rates (LBR) or clinical pregnancy rates (CPR)?
- Does untreated SCH affect developmental outcomes?
- When to test for antibodies?

Rating Scheme for the Strength of the Recommendations

Strength of Evidence

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

Cost Analysis

While a cost-effectiveness study suggested a cost-risk benefit, subsequent randomized trials found there was no benefit to universal screening for subclinical hypothyroidism (SCH) in pregnancy.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document was reviewed by American Society for Reproductive Medicine members, and their input was considered in the preparation of the final document.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- One observational study showed a nonstatistically significant improvement in miscarriage rates when treatment was initiated with a thyroid-stimulating hormone (TSH) level of >2.5 mIU/L.
- Levothyroxine treatment may improve pregnancy outcomes in women with positive thyroid antibodies, especially if the TSH level is over 2.5 mIU/L.

Potential Harms

See the original guideline document for discussion of overall benefit vs risk for specific recommendations.

Qualifying Statements

Qualifying Statements

This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Sep

Guideline Developer(s)

American Society for Reproductive Medicine - Nonprofit Organization

Source(s) of Funding

American Society for Reproductive Medicine

Guideline Committee

Practice Committee of the American Society for Reproductive Medicine

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Financial Disclosures/Conflicts of Interest

All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat

patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the American Society for Reproductive Medicine Web site .

Availability of Companion Documents

The following is available:

- Continuing medical education (CME) credit related to this guideline is available from the American Society for Reproductive Medicine Web site .

Patient Resources

The following is available:

- Hypothyroidism and pregnancy: what should I know? Fact sheet. Birmingham (AL): American Society for Reproductive Medicine; 2015. 1 p. Available from the ReproductiveFacts.org Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on April 26, 2016. The information was verified by the guideline developer on June 15, 2016.

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